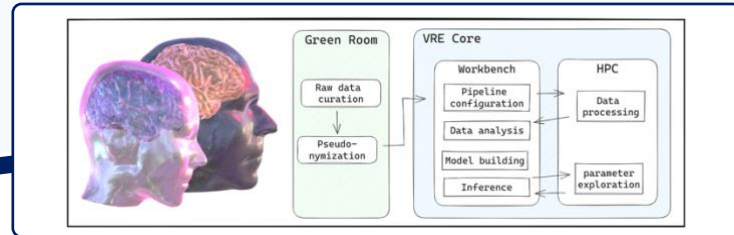




# VirtualBrainCloud

Personalized Recommendations for Neurodegenerative Disease



[www.VirtualBrainCloud-2020.eu](http://www.VirtualBrainCloud-2020.eu)

## Public deliverable report

D8.3: Validated Use Case of a brain simulation platform for NDD, usable by scientists and clinicians, for subsequent refined clinical studies towards development of therapeutic targets associated with basic physiological mechanisms

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Dissemination level:	<b>public</b>
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## 1. Introduction

The brain simulation platform developed by The VirtualBrainCloud (TVB-Cloud) project provides a cloud-based environment for execution of scientific and clinical studies centered around personalized brain modeling approaches. The offered collection of integrated tools and services allows for secure research data collection, analysis and sharing. In this deliverable we provide a validated use case for the platform demonstrating its use for a research workflow in the context of Neuro Degenerative Disease (NDD).

The use case presented here instantiates the workflow for construction of individualized brain network models and their use in the inference framework applied to the case of NDD (Yaçınkaya et al., 2023), building on the workflow presented in the deliverable D8.2<sup>1</sup>, using the tools presented in D8.1<sup>2</sup>. The components and resources available in the VRE support the execution of the individual steps and provide an integrated environment where such work can be performed end-to-end.

In this deliverable we present a use case of the brain simulation platform for NDD detailing the individual steps of data feature analysis, model building, simulation, and simulation-based inference. These steps make use of the VRE features for data analytics and HPC access and demonstrate their usage in a complete scientific workflow. As such, the use case provides a reusable template for researchers aiming to use VRE to execute their scientific vision.

## 2. Partners involved

AMU, Charité

## 3. Work performed and results

### 3.1. Workflow overview

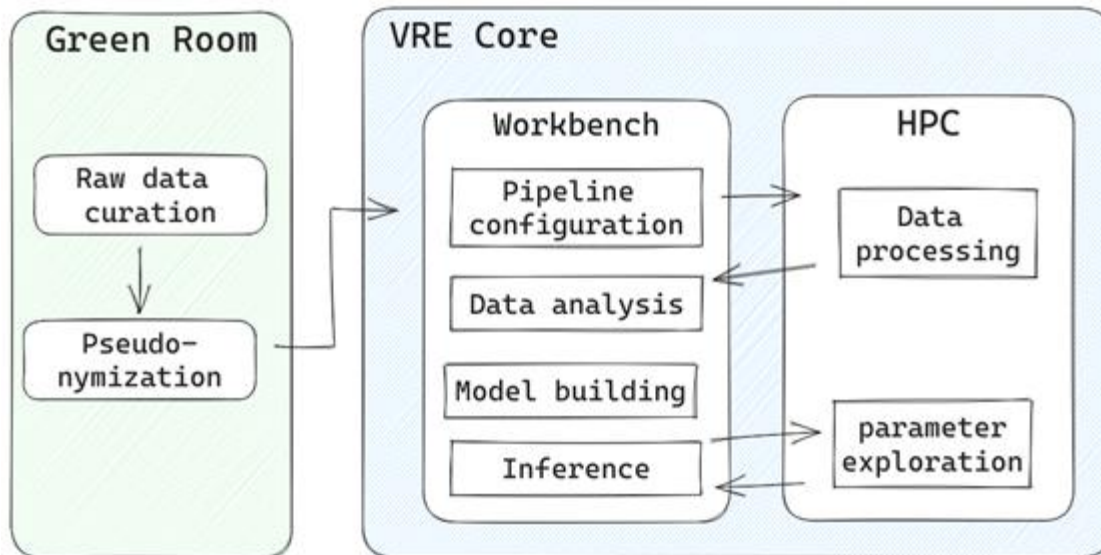
The VRE provides tools and infrastructure to support the complete end-to-end workflow of a research project centered around personalized brain simulation approaches. Such workflow starts with the raw MRI data of individual subjects, which is uploaded to the Green Room. Here, after the basic curation steps aiming to standardize the data and perform quality control, the dataset is stripped of personal information unnecessary for subsequent processing and transferred to the VRE Core after project administrator approval. The Workbench tools such as remote desktop gateway, interactive computing environment, a data exploration platform and an attached HPC cluster can be used to carry out the actual steps of the workflow. In what follows, we detail execution of the steps pertaining to the model building and inference parts of the study on a cohort of NDD subjects and healthy controls (Yaçınkaya et al., 2023), as described in deliverable D8.2<sup>3</sup>.

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<sup>1</sup> D8.2: TVB human models will be made available. We will identify the biophysical terms in the TVB models that are altered in NDD as compared to healthy individuals, and in relation to cognitive status

<sup>2</sup> D8.1: Validated and benchmarked data fitting workflow will be provided as a software for brain model personalization

<sup>3</sup> D8.2: TVB human models will be made available. We will identify the biophysical terms in the TVB models that are altered in NDD as compared to healthy individuals, and in relation to cognitive status



**Figure 1:** Workflow overview of the use case in the Virtual Research Environment. The raw data is curated and pseudonymized in the green room and then transferred to the VRE Core. There the steps of the use case are realized mainly in the Workbench, while offloading compute-intensive steps to the High-Performance Computing cluster.

## 3.2. Technical Specification

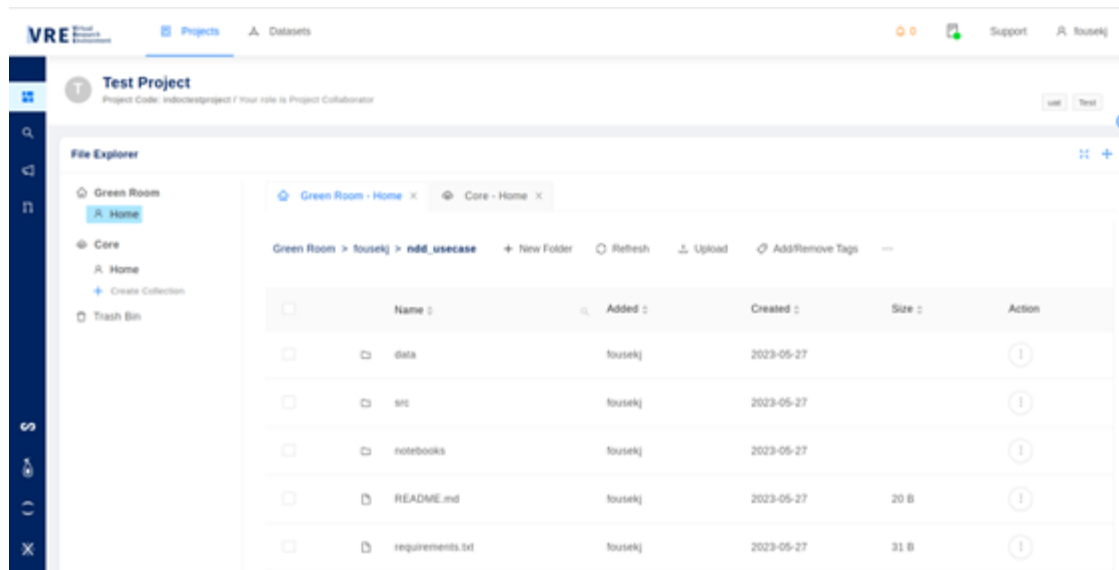
In this section we detail the implementation of the use case workflow in the VRE. The use case consists of a mixture of interactive computational notebooks, operations in the VRE web interface and command line actions performed in the HPC cluster. This mixture is in line with the common skillset of a computational neuroscientist and makes use of familiar tools and approaches.

### 3.2.1. Setting up the workspace

The workflow described here starts from the data derivatives for brain network modeling: structural connectivity matrices and fMRI regional timeseries. These result from applying pipelines to the neuroimaging data such as those described in D3.2<sup>4</sup>. The description of the use case below starts after these pipelines were completed and the respective data derivatives were uploaded to the Core storage of the VRE project.

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<sup>4</sup> D3.2: Most appropriate RS-processing pipelines for TVB modelling finished



**Figure 2:** Web interface of the VRE for managing the project. Data transfers can be initiated here, as well as the launch of the Workbench tools.

The main bulk of the use case analysis is performed in the VRE workbench, in particular the JupyterLab environment. The version control repository of the use case is the backbone of the project allowing us to efficiently move between the different computing environments (local, VRE workbench and VRE HPC) while keeping track of the changes. This also extends to the data with the help of DVC ([Data Version Control](#)) adding the provenance information of each of the data processing steps done in the workbench and HPC space.

The first step of the analysis is then to clone the repository in the VRE Workbench and use the VRE Command Line Tool to download the input data from Core storage and commit them to the version control.

### 3.2.2. Data analysis and brain modeling

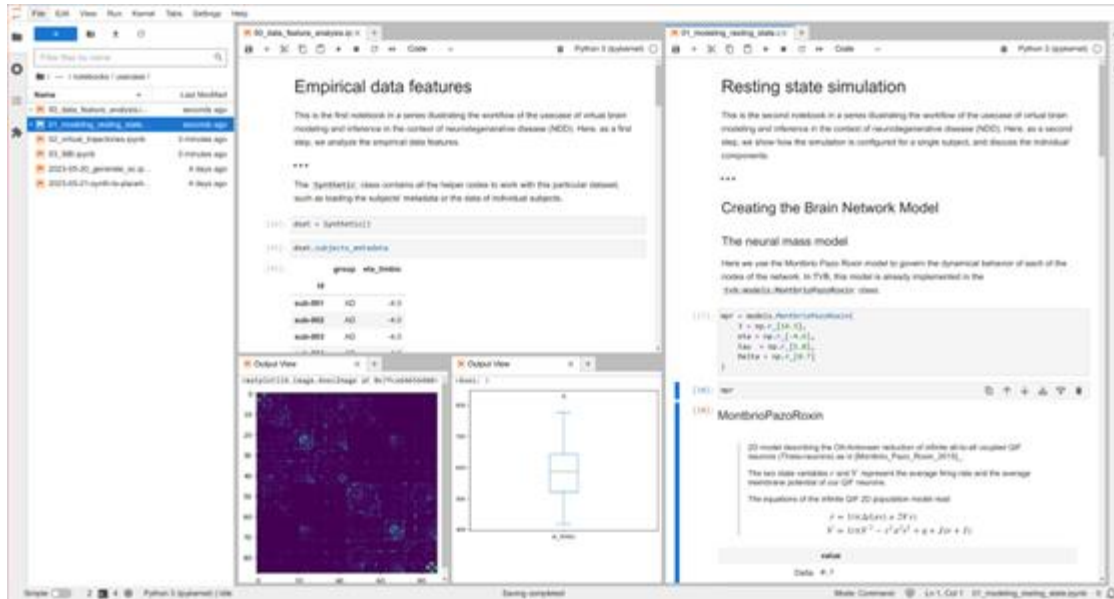
The use case workflow starts with empirical data exploration. A battery of summary statistics is evaluated on the functional and structural data and compared between the groups. In particular, the functions to compute a broad battery of metrics based in functional connectivity and functional connectivity dynamics are provided in the use case code, however the project structure allows for easy extension with additional summary statistics. This is necessary as finding suitable set of data features for a particular combination of a dataset and research question is a crucial step.

The second major step in the use case workflow is brain network modeling realized with The Virtual Brain (TVB) simulator (Sanz-Leon et al., 2013, Schirner et al., 2022). Configuration of the model, adjustments of how the connectivity data is used to construct the network (e.g. scaling) and basic parameter calibration is best performed in the interactive computing environment of the Jupyterlab. Once the working point of the model has been identified, systematic explorations of the parameter space are performed, e.g. with respect to a hypothesized mechanistic change across the groups.

Here we implement in the model different potential effects of AD progression – no change beside the individualized connectome, increase in excitability of the limbic system, and attenuation of the afferent connectivity of the limbic system. Each of these scenarios is then evaluated *in silico* on the cohort level



with respect to the group differences in the summary statistics identified as statistically significant in the first step.



**Figure 3:** Interactive computing environment of the VRE supports the data analysis and modeling steps of the use case workflow. The individual steps of the workflow are realized as Jupyter notebooks interleaving documentation, visualization and code snippets.

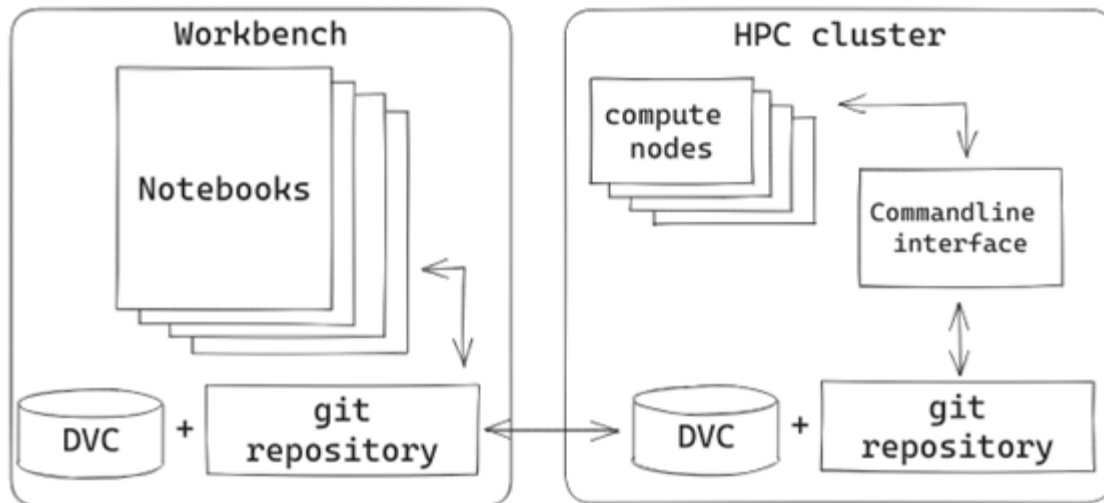
### 3.2.3. Computation offloading

The systematic parameter exploration steps described in the previous section necessitate running numerous simulations across a given range of parameters. To execute these workloads on the HPC infrastructure, we make use of the tools contained in the TVB-inversion package developed as a part of the D8.1<sup>5</sup>. TVB-inversion provides several backends for executing the simulations, in this case we make use of the batch backend as the HPC gateway available in the VRE provides access to a SLURM-based system.

First, to describe the work to be done, a simulation sequence is configured by the user, which is composed of a simulator template together with the lists of parameters and parameter values for each work item. Setting such data structures in the code is very flexible and allows the user to customize this configuration exactly to their needs.

Next, based on this configuration, a dedicated experiment folder is created in the repository containing the necessary code and parameter tables, and synced with the HPC cluster via the ssh access. There, the command-line interface of the experiment is used to submit the work to the compute nodes. After the simulations are completed, the data is committed to DVC together with the execution logs for provenance purposes, and synchronized back to the workbench.

<sup>5</sup> D8.1: Validated and benchmarked data fitting workflow will be provided as a software for brain model personalization.



**Figure 4:** Schema of the workflow for offloading computation to the HPC cluster from the VRE. The code and data is configured in the Workbench and committed to the git repository augmented with Data Version Control. After transfer to the HPC cluster, the workload is spread using the generated command line scripts.

### 3.2.4. Simulation based inference

Having identified the relevant structural and functional empirical data features, and the mechanistic hypothesis in the model, we can combine all the ingredients in the Bayesian inference framework using the Simulation Based Inference (SBI; Gonçalves et al., 2020). SBI allows for full posterior distribution parameter estimation for a black-box simulator using a deep neural network estimator trained to provide the relationship between the parameters of the model, and a set of selected descriptive statistics of the observed and simulated data.

The procedure is roughly split into three steps:

1. Simulations using parameters drawn from prior distributions
2. Training the deep neural estimator
3. Computing the posterior density with respect to the empirical observables.

Definition of the priors and configuration of the inference is facilitated by the TVB-inversion package and done interactively in the Jupyterlab of the Workbench. While the subsequent sampling from the prior distributions is computationally demanding due to the large number of required simulations, we can use the computation offloading described in the previous section to leverage the compute resources available in the VRE HPC gateway. The estimator training and the inference steps are then again performed in the interactive session which provide sufficient memory and compute power.

Lastly, the inference with SBI as implemented in the TVB-inversion allows for evaluation of the scheme with respect to identifiability as detailed in Deliverable D8.1<sup>6</sup>.

### 3.2.5. How to access the Use Case

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<sup>6</sup> D8.1: Validated and benchmarked data fitting workflow will be provided as a software for brain model personalization.



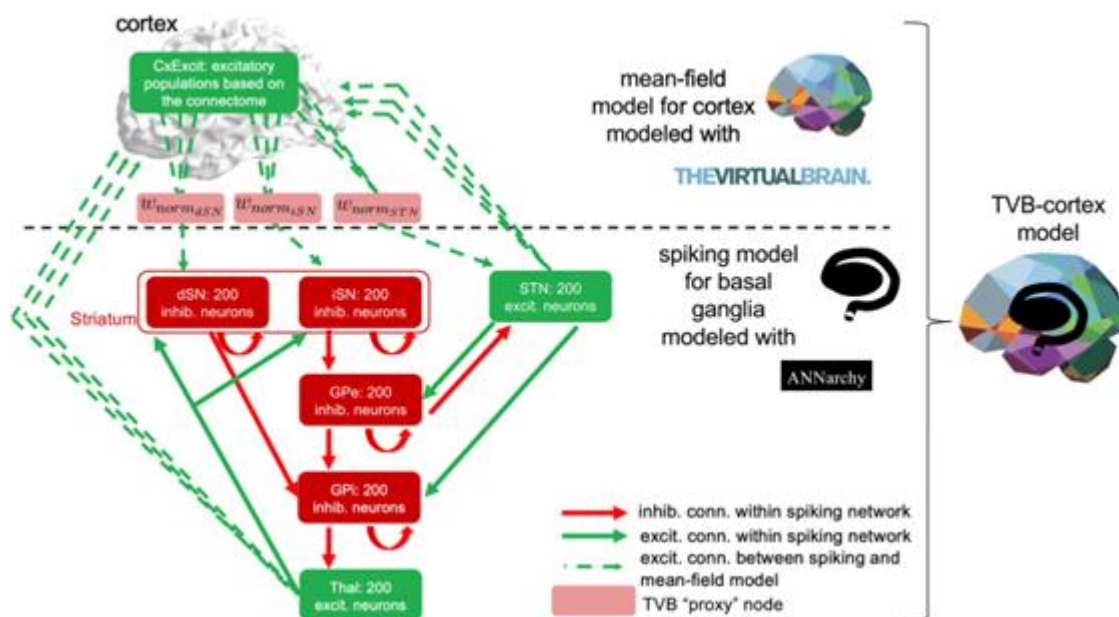
The implementation of the use case is freely available in the repository linked below. The repository also contains completely synthetic datasets which can be used in the test project by new-coming users to lower the barrier for onboarding and training.

- [https://github.com/ins-amu/ndd\\_usecase](https://github.com/ins-amu/ndd_usecase)

### 3.2.6. Validation

The workflow presented in this use case was validated in another paradigm – healthy aging (Lavanga et al., 2022). There, the same model and workflow was applied to a different dataset (Caspers et al., 2014) to study the hypothesized mechanisms of healthy aging. The workflow shares many of the involved components and the overall structure (Lavanga et al., 2023) validating the approach based on the Simulation Based Inference, value of the FCD-based measures of fluidity, and cohort- and mechanism-based approach to studying brain-health trajectories.

In a broader context, the TVB brain simulation platform was validated in additional works. The team at Charité developed and validated a model for deep brain stimulation (Meier et al. 2022). Here the TVB was extended towards a multi-scale simulator replacing regions of interest (basal ganglia and thalamus) with populations of spiking neuron models. The focus was on validation of the model with suitability for capturing relevant features in both the resting state and under stimulation.



**Figure 5:** Multi-scale model of DBS in Parkinson's Disease. Basal ganglia and thalamus replaced with detailed spiking neuron models, model dynamics validated against electrophysiological data (EEG, population spikes, LFP)

As this work was done using the software components and concepts aligned with the use case presented in detail in this deliverable, it provides a valuable resource for future users interested in recombining and adapting these approaches in their research.

## 4. Conclusion, next steps





The use case presented here demonstrates how the Virtual Research Environment can be leveraged as a brain simulation platform to execute a scientific research project. As such, it provides a real value to external users by offering reuse of data, models, complete workflows, and their components.

To increase the reach to potential users and to improve the findability of the workflow, we are currently going through the curation process of EBRAINS to get the model and template repository listed in the Knowledge Graph. In addition, validation on additional datasets will be pursued.

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